REMARKS

This amendment is responsive to the non-final Office Action mailed January 13, 2003. Original Claims 1-49 were subject to a restriction requirement which was made final, resulting in Claims 8-49 being withdrawn from consideration. Claims 1-7 were elected and are under examination in the present action. Claim 1 has been amended to incorporate features of former dependent Claims 3 and 7 (in addition to other features), and those claims are hereby cancelled. Support for the amendments to Claim 1 is apparent from original Claims 1, 3, and 7, and from the specification, e.g., at page 1, lines 19-24; page 4, lines 20-23; and page 7, lines 20-23. New Claim 50 is added to specifically recite preferred ligand recognition sequences discussed in the application, e.g., at page 17, lines 12-28. New Claim 51 is added to further specify recite the cleavability of the fusion proteins claimed, which are useful for the release and recovery of the protein of interest. Support for new Claim 51 is found throughout the specification, e.g., at page 5, lines 9-19, and Example iv, pages 40-41 (see, esp. Table 7).

Applicants wish to thank Examiner Patterson for granting the telephone interview of Friday, April 11, 2003, to discuss this case with Applicants' representatives. The amendments herein and the following remarks address issues presented in the Office Action and discussed in the telephone interview.

Response to issues presented under 35 U.S.C. §112

Claims 1-7 stand rejected under 35 U.S.C. §112, first paragraph, as being deemed to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Particularly, the Examiner states: "It is not seen how applicants arrived at the limitations of the instant claims and for the reasons outlined *supra*, it is maintained that the limitations are not justified or enabled." Applicants request reconsideration.

In the Office Action, the Examiner states that "[f]ive rounds of this incubation with enterokinase were performed with increasing stringency and presumably the positive phage from the preceding round was used for the next round." (Office Action, paper no. 11, page 4). As clarified in the telephone interview, however, it is only in rounds 4 and 5 that the stringency of the screening was increased, i.e., by lowering the enterokinase concentration to which the streptavidin-bound, enterokinase susceptible phage were exposed. Pages 33-34 of the application describe how separate aliquots of phage were treated with 320 nM enterokinase and 1300 nM enterokinase in rounds 1-3; in round 4, the 320 nM phage isolates were treated with 65 nM enterokinase for 30 minutes, then an additional 90 minutes; and in round 5, the

30-minute phage isolates of round 4 were treated with either 10 nM or 30 nM enterokinase. As explained on page 33, the stringency of the isolation rounds was increased in this way to try to force a consensus in enterokinase cleavage sequence patterns in the phage recovered.

The crux of the Examiner's rejection appears to concern the fact that not all of the Round 5 isolates are covered by Claim 1, and, conversely, that some of the embodiments in Claim 1 were not isolated in Round 5. Additionally, the Examiner notes that the instant claims do not require that streptavidin binding sites be present, nor do they require a factor Xa cleavage site, "as was the case in the experimental phage displays." (Office Action, paper no. 11, page 4).

First, Applicants note that the enterokinase (EK) susceptible phage isolates of each round were all cleaved by enterokinase. Therefore, each of the sequences disclosed in Tables 1-4 is a functional enterokinase recognition sequence. Those individual EK recognition sequences are claimed directly in Claim 13. Round 5 was merely the most stringent screening condition.

The Examiner correctly notes that there is no example of threonine (Thr) in the Xaa_4 amino acid position, as recited in Claim 1, among the sequenced isolates in Table 4 (Round 5). Accordingly, the Examiner questions whether Applicants were in possession of the formula (1) polypeptide (Claim 1) at the time of filing. Applicants point out that EK recognition sequences including threonine at the Xaa_4 position are present in several Round 4 isolates, namely, SEQ ID NOs: 67, 72, 89, 128, and 133. (*See* Table 3, pages 36-37). Moreover, once the D-R motif was discovered, Applicants chemically synthesized additional enterokinase cleavage sites containing the D-R↑ motif to further test the rate and extent of cleavage. Of these five additionally synthesized test peptides, three contained the threonine-containing T-D-R↑ motif. (*See*, e.g., Table 6 and its context on pages 40-41; SEQ ID NOS: 199, 202, and 203). Additionally, of those five synthesized test cleavage sequences, all proved to be EK-cleavable, with test peptide GNY**TDR**↑MFI (SEQ ID NO: 199) showing a cleavage rate over twice as rapid as the known enterokinase recognition sequence GDDDDKI (*see*, SEQ ID NO: 197). (*See*, Tables 6-8 and their accompanying description, pages 40-42).

The particular parameters of the enterokinase recognition sequence of formula (1) recited in Claim 1 are derived from the teaching at the bottom of page 44 of the application, *viz.*:

> "Analysis of the sequence information from screening Rounds 4 and 5 was performed to detect preferences for amino acids at the positions upstream of the scissile bond, in order to select preferred EK cleavage

> sequences. For the most numerous group, i.e., cleavage sequences having the Asp-Arg motif at the P_2 and P_1 positions, an amino acid was regarded as preferred at a given position in the sequence if it occurred in five or more isolates. Where a phage residue occurred at a given position, it was not counted. From this analysis, a family of preferred EK recognitions sequences was defined having the following formula:
>
> Xaa_1-Xaa_2-Xaa_3-Xaa_4-Asp-Arg-Xaa_5 (SEQ ID NO:206),
>
> wherein Xaa_1 is an optional amino acid residue which, if present, is Ala, Asp, Glu, Phe, Gly, Ile, Asn, Ser, or Val; Xaa_2 is an optional amino acid residue which, if present, is Ala, Asp, Glu, His, Ile, Leu, Met, Gln, or Ser; Xaa_3 is an optional amino acid residue which, if present, is Asp, Glu, Phe, His, Ile, Met, Asn, Pro, Val, or Trp; Xaa_4 is Ala, Asp, Glu, or Thr; and Xaa_5 can be any amino acid residue."

As explained during the telephone interview, the genus of formula (1) of Claim 1 was derived by careful analysis of the sequence data of dozens of actual enterokinase cleavage sequences isolated by the inventors. At each variable amino acid position in formula (1), at least five cleavage sequences had been discovered having an amino acid at that position belonging to the amino acid set defined for that variable amino acid. The inventors concluded and taught that this was strong evidence that each of those amino acids selected from that set would operate in that position to support enterokinase recognition and cleavage adjacent the downstream Asp-Arg dipepetide.

From the disclosure at page 44-45, it is clear that Applicants were not only in possession of the subject matter of the present claims, but were also aware of, and distinctly teach and enable, the novel enterokinase recognition sequences as defined in of Claim 1, formula (1).

The Examiner also notes that Claims 1-7 did not require streptavidin binding sites to be present and do not require a factor Xa cleavage site, "as was the case in the experimental phage displays." (Office Action, paper no. 11, page 4). However, it is not a requirement of 35 U.S.C. §112 that the claims reflect the experimental conditions leading to the discovery of the invention. The object of the instant invention was to provide novel enterokinase recognition sequences, and these are specifically and clearly defined in the claims. Thus, no issue under 35 U.S.C. §112 is seen to arise from the absence of any particular experimental conditions from the claims.

One who discovers a new product is entitled to claim *the product*; he or she is not limited to, or even required to recite in the claims, *how* the product was discovered. Those details belong in the

specification and are required for purposes of teaching one of skill in the art how to make and use the invention; such details do not, however, belong in the claims. As the CAFC has straightforwardly stated, "Specifications teach. Claims claim." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 585, n.14 (Fed. Cir. 1985).

Notwithstanding the foregoing, Applicants note that pending Claim 1 has been amended herein to incorporate the recitation of original Claims 3 and 7, and thus the amended claims specifically recite an enterokinase-cleavable fusion protein having a ligand binding site and a protein of interest included in the recited polypeptide (1). The Examiner may regard this as relevant to the comment comparing the present claims with the experimental phage display, even though Applicants regard this as presenting no issue under 35 U.S.C. §112.

Additionally, during the telephone interview, the Examiner expressed concern over Claim 1 as being potentially non-enabled in respect of the numerous amino acid variations and combinations encompassed by the claim, arguing that certain combinations may in fact be inoperable. Applicants note that the inclusion of each of the amino acid choices for the variable amino acids within formula (1) is supported by at least five examples of enterkinase recognition sites set forth in Tables 1-4, and Applicants believe this is ample basis for their teaching that all of the encompassed sequences of formula (1) will be operable. As Applicants discuss above, and discussed earlier during the telephone interview, the particular parameters of the enterokinase recognition sequence recited in Claim 1 were derived from actual isolated examples. (*See*, the bottom of page 44 of the specification.)

Furthermore, it is also the case that it is not a function of claims to exclude each and every potentially inoperable embodiment. Applicants believe that all combinations provided for in Claim 1 are operable; however, all covered embodiments need not be operable in order for Claim 1 to be enabled. The Federal Circuit has affirmed:

> "Patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C.§112...It is impractical and unreasonable to require a patentee to set out an extended list of precise combinations and formulae since one skilled in the art would avoid obvious inoperative combinations." *Hybritech, Inc. v. Abbott Laboratories*, 4 USPQ2d 1001, 1012 (C.D. Calif. 1987), *aff'd*, 849 F.2d 1074, 3 USPQ2d 1302 (Fed. Cir. 1987)

Applicants disclose numerous working embodiments of the present invention (*see,* e.g., Tables 1-6). Moreover, Applicants experiments were conducted to discover a consensus in enterokinase cleavage sequence patterns. As discussed on pages 44-45, the amino acids recited in Claim 1 were considered especially likely to support enterokinase cleavage at the Arg-X_5 scissile bond if, among the stringently screening isolates, they appeared 5 or more times at that position among the round 4 and 5 isolates. Thus, it is clear that Applicants have not only enabled numerous combinations, but have also focused their claims on the most likely sequences to, in fact, be operable. Viewed in light of this disclosure, the sequences encompassed by formula (1) are well-based on the data of the application, and as such they are submitted to fulfill the requirements of 35 U.S.C. §112 with regard to operability.

For the foregoing reasons, removal of the rejections under 35 U.S.C. §112 is believed to be in order.

Response to issues presented under 35 U.S.C. §102 and §103

In the Office Action, Claims 1, 6, and 7 stand rejected under 35 U.S.C. §102(b) as being anticipated by any of Denhez et al. (1994) *J. Biol. Chem.* 269(23):16170-16179 (hereinafter *Denhez*); Escriva et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:6803-6808 (hereinafter *Escriva*); Dear et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:4431-4435 (hereinafter *Dear*); Hollander et al. (1996) *Nucleic Acids Research* 24(9):1589-1593 (hereinafter *Hollander*); Kerfeld et al. (1994) *Biochemistry* 33:2178-2184 (hereinafter *Kerfeld*); and Morris et al. (1995) *J. Bacteriology* 177(23):6825-6831 (hereinafter *Morris*). Similarly, Claims 1 and 3-7 stand rejected under 35 U.S.C. §102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. §103(a) as obvious over, *Denhez*, *Escriva*, *Dear*, *Hollander*, *Kerfeld*, or *Morris*.

A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. Whereas the references of record fail to disclose or suggest aspects of the invention that are particularly and distinctly claimed, reconsideration and withdrawal of the rejections under 35 U.S.C. §102 are requested.

First and foremost, Applicants note that none of the references cited teach novel EK recognition sequences. They are merely being relied upon as allegedly anticipatory art because they disclose one of the following sequences located somewhere within a larger polypeptide: ADR, DDR, EDR, or TDR. However, none of the references contains any teaching or suggestion that any of the disclosed proteins is

recognized or cleaved at that sequence by enterokinase. In the present case, the Examiner cannot presume that any protein that includes a ADR, DDR, EDR, or TDR motif will be cleaved by enterokinase for the purposes of examining Applicants' claims, because only Applicants' own disclosure teaches these sequences as EK recognition sequences.

In any event, before Applicants specifically address the Examiner's reasons for citing the aforementioned references, it is respectfully pointed out that the amendments detailed herein are sufficient to avoid all of the references of record. First, the claims have been amended to specifically encompass only "non-naturally occurring enterokinase-cleavable fusion proteins". This expressly excludes all of the naturally occurring, bacterial, parasitic and mammalian proteins discussed in the references.

It appears the Examiner contends that some of the EK recognition sequences have been found within non-relevant, larger proteins, and presumes they are cleavable by enterokinase (as taught only by Applicants) due to an inherent property of the embedded sequence. This argument, however, is without merit, as inherency cannot be based on the knowledge of the inventor. Rather, facts asserted to be inherent in the prior art must be shown by evidence *from* the prior art. (*See, In re Dembiczak*, 175 f.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher.")

A rejection under 35 U.S.C. §102 cannot be based on the probability of inherency. As the CAFC has stated:

> "To serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the *missing descriptive matter is* ***necessarily present*** in the thing described in the reference, and ***that it would be so recognized by persons of ordinary skill... Inherency ... may not be established by probabilities or possibilities.*** *The mere fact that a certain thing* ***may*** *result from a given set of circumstances is not sufficient.*" *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991) (citations omitted) (emphasis added).

In the present case, none of the cited art teaches enterokinase recognition sequences. Thus, the question is not whether the cited art inherently contains an EK cleavable sequence, but rather whether one skilled in the art would read the cited references as inherently disclosing enterokinase recognition sequences. (*See, Rosco, Inc. v Mirror Lite Co.*, 304 F.3d 1373, 64 USPQ2d 1676 (Fed. Cir. 2002).)

Applying the language of *Continental Can* in the present case, the "missing descriptive matter" that must be "necessarily present" in the cited art is the property of enterokinase recognition and cleavage. And the Examiner must show "that it would be so recognized by persons of ordinary skill" that enterokinase recognition "is necessarily present" in the sequences cited by the Examiner. But this is not the case: No one in the art prior to Applicants' invention could possibly associate those cited sequences with enterokinase recognition; moreover due to protein folding, glycosylation, etc. the sequence cited by the Examiner in the reference proteins might be occluded or incapable of enzymatic recognition. Even considering Applicants' discovery, it is only a *possibility* that the embedded sequences in the references recognize enterokinase. On the other hand, as claimed by Applicants, enterokinase recognition of the fusion protein is a required property.

In summary, the Examiner points to no evidence that one of ordinary skill in the art could read the cited references as teaching enterokinase-cleavable proteins. Instead, the Examiner incorrectly relies on the *teachings of the Applicant's own specification*, rather than the knowledge of one skilled in the art, to show that the subject amino acid sequences have the ability to act as enterokinase recognition sequences. Furthermore, the Examiner regards the present claims as anticipated based only on a *possibility* that enterokinase can even *access* the natural, embedded sequences of the citations, not on a known scientific certainty that enterokinase does access and cleave any of those sequences as found in nature. The law allows none of these presumptions. As stated above, a rejection based on inherency requires that the missing descriptive material is necessarily present in the prior art, and that it would be so recognized by persons or ordinary skill in the art. The *possibility* that the cited proteins *might* be recognized and cleaved by enterokinase does not support the conclusion that those properties are inherent in the presence of the sequences.

During the telephone interview, the Examiner referred to the decision in *In Re Best*, (562 F.2d 1252, 195 USPQ 430 (CCPA 1977)) as grounds for shifting the burden to the Applicants to prove that the various references do not inherently anticipate the Applicants' invention. The present case, however, is not like *In re Best*. In that case, the fact that a composition heated to a certain temperature would *inherently* return to ambient temperature once the heat was removed was the property that the CCPA decided must of necessity occur. Here, the enterokinase susceptibility argued by the Examiner to be inherent in the cited proteins is not as predictable or as certain as cooling to room temperature. As the Board of Patent Appeals and Interferences has held, before the burden of distinguishing a claimed composition from cited art shifts to the applicant, the examiner must establish that the inherent link to a

recited function was known in the art: "**[T]he examiner must provide s me evidence r scientific reasoning t establish the reasonableness of the examiner's belief that the functional limitation *is an inherent characteristic of the prior art* before the applicant can be put through this burdensome task.**" *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI, 1986).

Moreover, inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

For the foregoing reasons, the invention as claimed in Claim 1, namely, an EK-cleavable fusion protein comprising a binding domain, an enterokinase recognition sequence having a specified amino acid structure, and a protein of interest, is not found in any of the prior art references of record. Hence, none of the cited references can anticipate Claim 1 or claims depending therefrom as a matter of law.

In view of the amendments to the claims herein and the foregoing remarks, reconsideration and withdrawal of the rejections of Claims 1 and 3-7 under 35 U.S.C. §102(b) and/or 35 U.S.C. §103(a) are respectfully requested.

Every effort has been made to advance the case to allowance, to particularly and distinctly define the subject matter of the invention, and to distinguish the invention over the prior art of record. In view of the amendments herein and the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested. The Examiner is requested to contact the undersigned by telephone if any further issues are deemed to remain.

Respectfully submitted,

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Michael R. Wesolowski

Appendix A

COMPLETE CLAIMS IN Ser. No. 09/884,767
(marked set showing deletions ~~by strikethrough~~ and additions by underlining)

1. **(Currently amended)** A non-naturally occurring enterokinase-cleavable fusion protein ~~polypeptide~~ comprising a polypeptide comprising ~~an enterokinase recognition sequence and having~~ the formula:

(1) Z_1-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Asp-Arg-Xaa_5-Z_2 (SEQ ID NO:1),

wherein

(a) Z_1 is a ligand recognition sequence;

(b) Xaa_1-Xaa_2-Xaa_3-Xaa_4-Asp-Arg is an enterkinase recognition sequence, in which ~~wherein~~

Xaa_1 is ~~an optional amino acid residue which, if present, is~~ Ala, Asp, Glu, Phe, Gly, Ile, Asn, Ser, or Val;

Xaa_2 is ~~an optional amino acid residue which, if present, is~~ Ala, Asp, Glu, His, Ile, Leu, Met, Gln, or Ser;

Xaa_3 is ~~an optional amino acid residue which, if present, is~~ Asp, Glu, Phe, His, Ile, Met, Asn, Pro, Val, or Trp;

Xaa_4 is Ala, Asp, Glu, or Thr; and

~~Xaa5 can be any amino acid residue; and~~

~~wherein~~

(c) Xaa_5-Z_2 is a protein of interest, in which X_5 can be any amino acid ~~Z_1 and Z_2 are both optional and are, independently, polypeptides of one or more amino acids~~.

2. **(Currently amended)** The ~~polypeptide~~ fusion protein of Claim 1, wherein

Xaa_1 is Asp,

Xaa_2 is Ile,

Xaa_3 is Asn, Xaa_4 is Asp,

and Xaa_5 is Met, Thr, Ser, Ala, Asp, Leu, Phe, Asn, Trp, Ile, Gln, Glu, His, Val, Gly, or Tyr.

3. **(Cancelled)** ~~The polypeptide of Claim 1, wherein Z_1 is a ligand recognition sequence.~~

4. **(Currently amended)** The ~~polypeptide~~ fusion protein of Claim 1, wherein ligand recognition sequence Z_1 is a streptavidin binding domain.

5. **(Original)** The fusion protein of Claim 4, wherein the streptavidin binding domain is selected from the sequences: His-Pro-Gln-Phe (SEQ ID NO:6), Cys-His-Pro-Gln-Phe-Cys (SEQ ID NO:5), Cys-His-Pro-Gln-Phe-Cys-Ser-Trp-Arg (SEQ ID NO:7), Trp-His-Pro-Gln-Phe-Ser-Ser (SEQ ID NO:210), Pro-Cys-His-Pro-Gln-Phe-Pro-Arg-Cys-Tyr (SEQ ID NO:211), and tandemly arranged combinations and repeats thereof.

6. **(Cancelled)** ~~The polypeptide of Claim 1, wherein Z_2 is a protein of interest.~~

7. **(Cancelled)** ~~The polypeptide of Claim 1, wherein the polypeptide Xaa_5-Z_2 is a protein of interest.~~

8-49. **(Cancelled as non-elected)**

50. **(New)** The fusion protein according to Claim 1, wherein said ligand recognition sequence Z_1 is selected from the group consisting of: streptavidin, avidin, an antibody, a peptide antigen recognized by an antibody, the Myc-tag, the Flag peptide, the KT3 epitope peptide, an α-tubulin epitope peptide, a polyhistidine tag, a chitin binding domain, maltose binding protein (MBP), and the T7 gene 10-protein peptide tag.

51. **(New)** The fusion protein according to Claim 1, wherein incubation of said polypeptide (SEQ ID NO:1) with enterokinase yields the protein of interest Xaa_5-Z_2.